Application No. 10/789,312
Filed: February 27, 2004
TC Art Unit: 1644
Confirmation No.: 9773

REMARKS

Claims 18-22, 24-28, 30-42, and 44-47 will be pending upon entry of these amendments. Claims 1-17 were previously cancelled, and claims 23, 29, and 43 are canceled herein. Claims 18-21, 25, 31-39, and 46-47 are withdrawn. Claims 22, 26, 30, 40-42, and 44 have been amended. Claims 22, 24, 26-28, 30, 40-42, and 44-45 are currently under examination.

Claim Amendments

Claims 22, 30, and 40 have been amended to specify that the expressed ALP protein is a glycoprotein. Support is found in the specification and drawings, for example in Fig. 5 and the description thereof at page 6, lines 16-22, and in the experiment described in Example 3 at page 10, all of which describe a glycosylated ALP protein.

Claim 26 has been amended to delete reference to a canceled base claim.

Claims 40, 41, and 44 have been amended to clarify that expression takes place in a host cell.

Claim 42 has been amended to limit the microorganism host cell to yeast in this dependent claim.

The amendments do not introduce any new matter.

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Interview

Applicants thank the Examiners Rooney and Haddad for the courtesy of the telephone interview on August 21, 2007, in which the enablement rejection was discussed. The role of the carbohydrate portion of ALP in its allergenicity, as evidenced by the post-filing Arif et al. publication (see below), was discussed.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 22-24, 26-30, and 40-45 are rejected as allegedly lacking enablement. The rejection is respectfully traversed.

The Office Action recognizes that the specification is enabling for the nucleic acid sequence of SEQ ID NO:1 encoding the protein of SEQ ID NO:5 and a method of producing the protein of SEQ ID NO:5 using the nucleic acid of SEQ ID NO:1. However, the Office Action alleges that the specification is not enabling for nucleic acids encoding conservative amino acid substitutions of SEQ ID NO:5. The Office Action also appears to suggest that the specification lacks enablement for a nucleic acid "comprising" a nucleotide sequence encoding SEQ ID NO:5. Finally, the Office Action alleges that certain of the methods of expressing a

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recombinant protein, for example the method of claim 40, are not enabled because the methods recite expression from a vector.

As a threshold matter, Applicants point out that the claims directed to methods of expressing a recombinant protein (e.g., claim 40 and its dependent claims) have been clarified by amendment to recite the use of a host cell. Applicants believe that the present claims recite enabled methods for expressing a recombinant protein.

The Examiner has maintained the position that undue experimentation would be required for one of ordinary skill in the art at the time of the invention to prepare nucleic acids encoding variants of SEQ ID NO:5 which include conservative amino acid substitutions and induce an allergic reaction to latex. The Office Action at page 4, final paragraph, states:

> The Examiner argues that there is tremendous variability in the importance of individual amino acids in protein sequences. Since the amino acid sequence of SEQ ID NO:5 is a key determinant of allergenic activity, single residue substitutions can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone.

Applicants disagree.

Applicants do not dispute that certain amino acids within a protein sequence are more important than others. However, the claims do not permit merely any amino acid substitution, but only

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conservative amino acid substitutions. Conservative substitutions, as generally understood in the art, imply replacement with amino acids having similar chemical properties, and which are therefore unlikely to alter protein structure or function. The categorization of amino acids by chemical property is well known in the art. For example, Applicants' recently issued European patent defines conservative amino acid substitutions as follows:

> Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of ALP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

EP1481991B1 at page 4, lines 24-29.

Applicants also do not dispute that single residue substitutions can have severe phenotypic effects. However, Applicants maintain that it is very unlikely that conservative amino acid substitutions would have such phenotypic effects.

Applicants disagree entirely with the Examiner's statement that "[t]here is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information

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alone." Methods were well known in the art at the time of filing for predicting, with reasonable accuracy, whether a given amino acid substitution would alter protein phenotype. The BLOSUM and PAM matrices are well known examples. Applicants have attached, as merely one representative example among many, a publication by Ng and Henikoff (Exhibit A, published by Genome Research at www.genome.org/cgi/doi/10.1101/gr.176601) entitled "Predicting Deleterious Amino Acid Substitutions." The authors present a tool called SIFT that can be used to predict whether a given amino acid substitution in a sequence will have a phenotypic effect. The authors comment that only in "exceptional cases" does a predicted neutral substitution reveal itself experimentally to have a deleterious effect. See Ng et al. at page 864, lines 5-10. Clearly, conservative amino acid substitutions with reasonably predictable phenotypic effects were well within the capability of the skilled artisan at the time of the invention.

The Examiner appears to have taken a rather extreme position, supported only by rare exceptions to the general considerations outlined above. Some of the instances cited by the Examiner do not even qualify as conservative amino acid substitutions; see, e.g., Burgess et al., substitution of lysine by glutamic acid (and changing a positive charge to a negative), Office Action at page

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4, final paragraph. The legal standard of enablement does not require 100% predictability. The legal standard is that Applicant must teach, in view of the knowledge of the ordinary skilled artisan at the time of filing, how to make and use the claimed invention without requiring undue experimentation. Applicants submit that providing SEQ ID NO:5, coupled with knowledge in the art of conservative amino acid substitutions, together with disclosure of a routine test to determine allergenicity of the expressed recombinant protein, would have been more than sufficient to allow the skilled person to make and use a large number of recombinant ALP variants according to the claims.

Further evidence that undue experimentation would not have been involved in preparing the claimed recombinant ALP allergens is found in the post-filing publication by Arif et al. (J. Biol. Chem. 279, 23933-23941 (2004), previously cited by the Examiner). Fig. 7 of Arif et al. demonstrates that IgE binding was lost upon deglycosylation of the protein, leading the authors to conclude that the IgE binding epitope lies within the carbohydrate moiety, i.e., not on the polypeptide itself. This fact reduces even further the likelihood that a conservative amino acid substitution made to SEQ ID NO:5 would result in loss of allergenicity, provided that the recombinant protein is glycosylated. For the

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further avoidance of doubt, the claims have been amended to require that recombinant ALP expressed from a claimed nucleic acid is allergenic as a glycoprotein.

Regarding the use of "comprising" language, as Applicants previously argued, it is further unlikely that the addition of nucleotides to either or both ends of a nucleotide sequence encoding SEQ ID NO:5 or conservative amino acid substitutions thereof would result in the loss of allergenicity, particularly in view of the glycosylation of the expressed polypeptide, which retains the IgE binding epitope.

Therefore, because the specification teaches how to make and use the full range of nucleic acid molecules covered by the subject claims, the withdrawal of this rejection is respectfully requested.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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